

Coronavirus Disease 2019 (COVID-19): A Perspective from China

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Summary

Radiologists understanding of clinical and chest CT imaging features of coronavirus disease 2019 (COVID-19) will help to detect the infection early and assess the disease course.

Essentials

- Coronavirus disease 2019 (COVID-19) presents with nonspecific clinical manifestations, so diagnosis depends on epidemiological factors including Wuhan exposure or close contact history.
- Typical CT findings of COVID-19 include peripherally distributed multifocal ground-glass opacities (GGOs) with patchy consolidations and posterior part or lower lobe involvement predilection
- Increasing numbers, extent, and density of GGOs on CT indicate disease progression.
- Thin-slice chest CT plays a vital role in early detection, observation, and disease evaluation.

Abstract

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection occurred in Wuhan, Hubei Province, China and spread across China and beyond. On February 12, 2020, WHO officially named the disease caused by the novel coronavirus as Coronavirus Disease 2019 (COVID-19). Since most COVID-19 infected patients were diagnosed with pneumonia and characteristic CT imaging patterns, radiological examinations have become vital in early diagnosis and assessment of disease course. To date, CT findings have been recommended as major evidence for clinical diagnosis of COVID-19 in Hubei, China. This review focuses on the etiology, epidemiology, and clinical symptoms of COVID-19, while highlighting the role of chest CT in prevention and disease control.

Abbreviations

ARDS= acute respiratory distress syndrome

COVID-19 = Coronavirus Disease 19

GGO = ground-glass opacity

MERS = Middle East respiratory syndrome

RT-PCR = reverse-transcription–polymerase-chain-reaction

SARS = severe acute respiratory syndrome

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Introduction

An ongoing outbreak of pneumonia associated with a novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported in Wuhan, Hubei province, China (1-3) in December 2019. In the following weeks, infections spread across China and other countries around the world (4-6). The Chinese public health, clinical, and scientific communities took prompt response to allow for timely recognition of the new virus and shared the viral gene sequence to the world (2,7). On January 30, 2020, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC) (8). On February 12, 2020, WHO named the disease caused by the novel coronavirus as Coronavirus Disease 2019 (COVID-19) (9). A group of international experts, with a range of specializations, has worked with Chinese counterparts to try to contain the outbreak (10).

At present, real-time reverse-transcription–polymerase-chain-reaction (RT-PCR) assay for COVID-19 has been developed and used in clinics. Although RT-PCR remains the reference standard to make a definitive diagnose of COVID-19 infection (11), the high false negative rate (12) and unavailability of RT-PCR assay in the early stage of the outbreak restricted prompt diagnosis of infected patients. Radiological examinations, especially thin slice chest CT, play an important role in fighting this infectious disease (13). Chest CT can identify the early phase lung infection (14-15) and prompt larger public health surveillance and response systems (16). Currently, chest CT findings have been recommended as major evidence for confirmed clinical diagnosis in Hubei, China. The addition of chest CT for diagnosis resulted in 14840 confirmed new cases (13332 clinically diagnosed cases) reported on February 13, 2020. Comprehensive and timely review of radiological role in fighting COVID-19 remains urgent and mandatory.

Etiology

In preliminary report, complete viral genome analysis reveals that the virus shares 88% sequence identity to two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses, but more distant from severe acute respiratory syndrome coronavirus (SARS-CoV) (17). Hence, it was temporarily called 2019-novel coronavirus (2019-nCoV). Coronavirus is an enveloped and single-stranded ribonucleic acid named for its solar corona like appearance due to 9-12 nm-long surface spikes (18). There are four major structural proteins encoded by the coronaviral genome on the envelope, one of which is the spike (S) protein that binds to angiotensin-converting enzyme 2 (ACE2) receptor and mediates subsequent fusion between the envelope and host cell membranes to aid viral entry into the host cell (19,20). On

February 11, 2020, the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses finally designated it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on phylogeny, taxonomy and established practice (21). Soon later, WHO named the disease caused by this coronavirus as Coronavirus Disease 2019 (COVID-19) (9). On the basis of current data, it seems that COVID-19 might be initially hosted by bats, and might have been transmitted to humans via pangolin (22) or other wild animals (17,23) sold at the Huanan seafood market but subsequent spread via human-to-human transmission.

Epidemiology

On December, 2019, the earliest symptom onset of confirmed patients appeared (24). At first, the morbidity remained low but reached a tipping point in the middle of January 2020. During the second half of this month, a remarkable increase of infected patients in affected cities occurred outside Hubei province because of the population movement before lunar Chinese New Year (25). Followed by an exponential growth until January 23, 2020, the outbreak spread to the other countries, attracting extensive attention around the world (**Figure 1**). Evidence of clusters of infected family members and medical workers confirmed the presence of human-to-human transmission (12) by droplets, contact and fomite (26-27). So far, there is no definite evidence for intrauterine infection (28). Current estimates are that COVID-19 has a median incubation period of 3 days (range 0 to 24 days), with potential asymptomatic transmission (26, 29). At the end of January 2020, WHO confirmed more than ten thousand cases infected with COVID-19 across China (30). On February 13, 2020, 13332 new clinically diagnosed cases were firstly reported from Hubei. Official reports included clinically diagnosed cases and laboratory-confirmed cases because chest CT findings are recommended as the major evidence for clinically confirmed cases by Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (trial Fifth version) by National Health and Health Commission of China in 2020 (13). As of February 19, 2020, this rose to a total of 74280 confirmed cases in China and 924 confirmed cases in 24 countries outside China, and a total of 2009 deaths globally (10) (**Figure 2**). To control COVID-19, effective prevention and control measurements must include early detection, diagnosis, treatment, and quarantine to block human-to-human transmission as well as reducing secondary infections among close contacts and health care workers (10).

Clinical Symptom Spectrum

Understanding the clinical symptoms of COVID-19 is important, although the clinical symptoms are indicated nonspecific. Common symptoms include fever, cough and myalgia or fatigue. Patients may initially present with diarrhea and nausea a few days prior to fever, suggesting

fever is dominant but not the premier symptom of infection. A small number of patients can have headache or hemoptysis (26,32) and even relatively asymptomatic (12). Affected older men with comorbidities are more likely to have respiratory failure due to severe alveolar damage (31). Disease onset may show rapid progression to organ dysfunction (e.g., shock, acute respiratory distress syndrome [ARDS], acute cardiac injury, and acute kidney injury) and even death in severe cases (1,32). Meanwhile, patients might show normal or lower white blood cell counts, lymphopenia, or thrombocytopenia, with extended activated thromboplastin time and increased C-reactive protein level (1,26,31-32). In short, a patient having fever and upper respiratory tract symptoms with lymphopenia or leukopenia should be suspected, especially for patients with Wuhan exposure or close contact history.

Diagnosis of COVID-19 Infection

The first task for the clinical diagnostic workflow is to confirm Wuhan exposure history or close contact with people from Wuhan or confirmed patients during the past two weeks. However, the number of the patients with unknown exposure history is increasing due to the rapid and wide spread of the disease. The National Health Commission of China (33,34) formulated the Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (trial sixth version) (**Table 1**) based on the recommendations of the World Health Organization (WHO) on severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (35-37). A patient with one exposure history and two clinical conditions is considered as suspected case. If there is no clear exposure history, suspected patients should meet 3 clinical conditions (**Table 1**). Based on the fifth trial edition (13), chest CT findings of viral pneumonia are regarded as evidence of *clinical diagnosis* of COVID-19 infection. However, the WHO did not accept CT without RT-PCR confirmation until February, 17, 2020 (38) and the most recently published Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (trial sixth version) has deleted the term of *clinical diagnosis* (34). The final *etiology diagnosis* of COVID-19 is necessary, which can be further confirmed by positive real-time RT-PCR assay for COVID-19 using respiratory or blood samples or by viral gene sequencing of respiratory or blood samples that are highly homologous with COVID-19. According to the clinical manifestations, confirmed patients are divided into mild, moderate, severe, and critical types (**Table 2**) (13,34, 39).

The Role of Radiology in Detection of COVID-19

Radiological examinations are of great importance in the early detection and management of COVID-19. Because chest radiography is not sensitive for the detection of ground-glass opacity (GGO) and may demonstrate normal findings in early stage of infection (16), it was not recommended as the first-line imaging modality for COVID-19. However, bilateral multifocal

consolidation (**Figure 3**) can be seen in severe patients, partially fused into massive consolidation with small pleural effusions and even presenting with “white lung” (11). Thin slice chest CT functions more effectively in early detection of COVID-19 pneumonia (12,16). The largest sample study to date showed that among 3665 confirmed cases, 95.5% (n=3498) patients were diagnosed as pneumonia (25). Pan et al (40) reviewed 21 confirmed patients who underwent repeated CT at approximately 4 day intervals and found that negative findings were revealed in four patients on early stage (0-4 days after onset of the initial symptom), but repeat chest CT showed lung abnormalities in all of these 4 patients.

CT Imaging Findings

To date, only five case series studies (16,40-43) and some case reports (44-54) have investigated the chest CT imaging features of COVID-19 pneumonia. COVID-19 pneumonia has nonspecific and various chest CT imaging features. The typical chest CT findings include multifocal bilateral GGOs with patchy consolidations, prominent peripherally subpleural distribution and preferred posterior part or lower lobe predilection (**Figures 4-9**) (14,55-56). GGO is a hazy increase in attenuation that appears in a variety of interstitial and alveolar processes with preservation of the bronchial and vascular margins (57), while consolidation is an area of opacification obscuring the margins of vessels and airway walls (58). In patients with COVID-19 pneumonia, focal or multifocal pure GGO (**Figures 4a, 5, 6b**) and GGO with reticular and/or interlobular septal thickening as typical crazy-paving pattern (**Figure 6a**) were often observed, while pure consolidation (**Figure 7**) was relatively less common or absent (16,40-42). Pure GGO lesions (**Figure 4a, 5, 9b**) can be the early appearance of COVID-19 pneumonia. Chung et al. (41) found one patient with an initial normal chest CT that evolved into a new solitary, rounded peripheral GGO after three days. The reversed CT halo sign defined as a rounded area of ground glass surrounded by a complete or almost complete ring of consolidation can also be observed (16,49). Pleural effusion, lung cavitation, lymphadenopathy and calcification are rarely reported (40-44,49-50). **Table 3** summarizes the characteristic chest CT imaging features of COVID-19 pneumonia.

Other diseases mimic COVID-19 pneumonia and should be differentiated, including community-acquired pneumonia such as streptococcus pneumonia, mycoplasma and chlamydia related pneumonia, and other coronavirus infections. Differential diagnosis is very important to early quarantine suspected patients with fever and reduce cross infection. **Table 4** shows typical clinical and imaging findings of COVID-19 mimics such as common cold, influenza, and other coronaviruses diseases including SARS and MERS (11,59-63). Wuhan exposure history or close contact with confirmed or suspected patients is an essential clue for the diagnosis. However, for patients with unknown epidemiological history, typical clinical and imaging appearance can indicate suspected COVID-19; RT-PCR test should be performed in

these patients. In summary, the diagnosis of COVID-19 should combine epidemiological history, clinical and imaging manifestations, and RT-PCR test (the reference standard).

The Value of Radiology in Prevention and Control of COVID-19

Although chest CT findings are nonspecific for COVID-19 detection, CT findings have been recommended as major evidence of *clinical diagnosis* in Hubei province by the National Health and Health Commission of China (13). RT-PCR positive for COVID-19 remains the reference standard (11), but RT-PCR results can be affected by sampling errors and low virus load (64-66). Previous SARS studies (67-69) showed that RT-PCR lacked sensitivity during the first five days of the disease. Current reports show that chest CT may demonstrate pneumonia but multiple RT-PCR tests of nasopharyngeal or throat swabs test negative (12,53,70-71), and Fang et al. (72) compared the detection rate of initial chest CT and RT-PCR and reported a higher detection rate for initial CT (50/51[98%]) than first RT-PCR (36/51[71%]) patients ($P<0.001$). Xie et al. found that of 167 patients evaluated, 3% (5/167) patients had initially negative RT-PCR but positive chest CT and both RT-PCR and CT were concordant for COVID-19 in 92.8% ($n=155/167$) patients (70). Furthermore, RT-PCR results must be checked by the Centers for Disease Control and Prevention (CDC) in the early stage of an outbreak, taking a longer time to confirm the final diagnosis (25). Thin slice chest CT is easy to perform, fast, and detects early COVID-19 pneumonia with high sensitivity, providing valuable information for further diagnosis, while aiding prevention and control of COVID-19.

CT can also assess the disease severity of COVID-19 to guide clinical management. Clinical observations showed (1) that intensive care unit (ICU) patients on admission often presented with bilateral multiple lobular and subsegmental consolidation, while non-ICU patients presented with bilateral GGOs and subsegmental consolidation. In severe patients, CT can demonstrate diffuse heterogeneous consolidation with GGOs in bilateral lungs with air bronchial sign and bronchiectasis (**Figure 9**), presenting as “white lung” when most lung lobes are affected (15). Patients also may present with thickening of interlobar septa and bilateral pleura with a small pleural effusion (11,56).

Additionally, CT surveils disease time course of COVID-19. Chung et al. (41) found that 7 of 8 patients showed marked progression presenting as increasing number, extent, and density of GGOs (**Figures 4, 9**). Pan et al (40) reviewed 21 confirmed and recovered patients who underwent repeated CT at approximately 4-day intervals and summarized four stages of the disease: early, progressive, peak, and absorption. They found that GGOs will rapidly grow, demonstrating consolidation and crazy-paving pattern as the disease progresses. The lesions will absorb without crazy-paving pattern on absorption stage, suggesting crazy-paving pattern

as another index to evaluate the disease course. The study by Song et al (42) concluded that greater consolidation indicated disease progression. Some case reports showed that smaller size, extent, and absorption of these lesions indicate the improvement (32,42,51-53).

Conclusion

In conclusion, characteristic chest CT imaging features and Wuhan exposure or close contact history, highly suggest COVID-19 pneumonia, although RT-PCR remains the reference standard. Typical CT features of COVID-19 pneumonia include multifocal bilateral GGOs with patchy consolidations, prominent peripherally subpleural distribution, and preferred posterior part or lower lobe predilection. Thin slice chest CT can help prompt diagnosis, guide clinical decision making, and monitor disease progression, playing a critical role in the early prevention and control of COVID-19. Special attention should be paid to the role of radiologists in fighting this new infectious disease.

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Tables

Table 1: Case Definition for Surveillance of Coronavirus Disease 2019 (COVID-19) by Chinese Health Commission

Suspected case

Present at least two of the following conditions of

- i. Fever and/or respiratory symptoms (eg, cough, myalgia, fatigue)
- ii. Imaging features of viral pneumonia
- iii. Normal or low white blood cell count or reduced lymphocyte in early onset

AND

One or more of the following exposures during the 14 days prior to onset of symptoms

- 1). Travel or residence history in Wuhan, other areas with recent local transmission of COVID-19, or the local community with confirmed patient
- 2). Close contact* with patient with laboratory-confirmed COVID-19 (positive for nucleic acid test)
- 3). Close contact with people from Wuhan or surrounding areas or local communities with fever or respiratory symptoms case report
- 4). Cluster onset

Patients without exposure history should meet all of conditions i, ii and iii.

Clinically diagnosed case (added in the trial fifth edition but deleted in the trial sixth edition)

The suspected case with typical imaging findings of pneumonia (only for Hubei)

Confirmed case

Suspected cases have at least one of the following etiological evidence

- i. Positive real-time fluorescence polymerase chain reaction of the patient's respiratory or blood specimen for COVID-19 nucleic acid
- ii. Viral gene sequences in respiratory or blood specimen are highly homologous to COVID-19

Data from Refs.^{13,33-34}

*Close contact is defined as healthcare-related exposures, including direct care for patients with confirmed COVID-19, collaboration with healthcare workers with confirmed COVID-19, visiting or staying in the same closed environment with patients with confirmed COVID-19, or members who live in the same family environment with patients with confirmed COVID-19.

Table 2: Criteria for Clinical Severity of Confirmed Coronavirus Disease 2019 (COVID-19) Pneumonia

Types	Findings
Mild	Mild clinical symptoms [fever <38°C (quelled without treatment), with or without cough, no dyspnea, no gasping, no chronic disease] No imaging findings of pneumonia
Moderate	Fever, respiratory symptoms, imaging findings of pneumonia
Severe	Meet any of the followings: a. Respiratory distress, RR ≥30 times/min b. SpO ₂ <93% at rest c. PaO ₂ /FiO ₂ ≤ 300 mmHg * Patients showing a rapid progression (>50%) on CT imaging within 24-48 hours should be managed as severe (added in the trial sixth edition)
Critical	Meet any of the followings: a. Respiratory failure, need mechanical assistance b. Shock c. “Extra pulmonary” organ failure, intensive care unit is needed

Data from Refs.^{13,34-39}

Abbreviations: RR: respiratory rate; SpO₂: oxygen saturation; PaO₂: partial pressure of oxygen; FiO₂: fraction of inspired oxygen

Table 3: Chest CT Imaging Features of Coronavirus Disease 2019 (COVID-19) Pneumonia

Ground glass opacities +/-consolidation	+++
Pure consolidation	+
Multiple lesions	+++
Bilateral involvement	+++
Posterior part / lower lobe predilection	+++
Peripheral / subpleural distribution	+++
Crazy-paving pattern	++
Air bronchogram	++
Reversed halo sign on high-resolution CT	+
Pleural effusion	+
Cavitation, calcification, lymphadenopathy	Absent

Data from Refs. 1,16,32,40-43,55-56

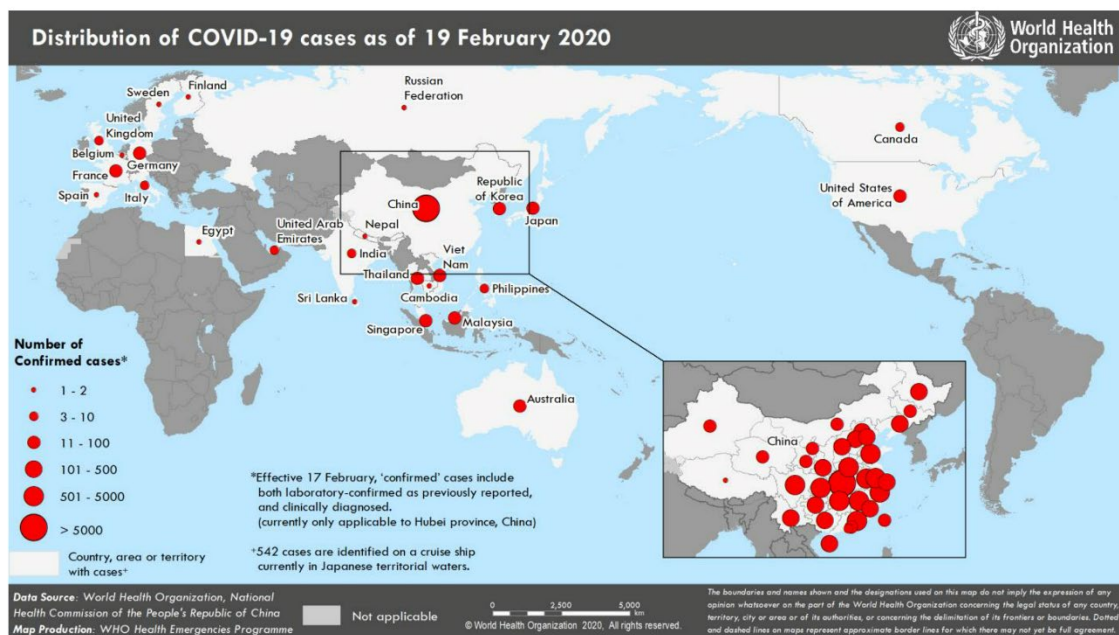
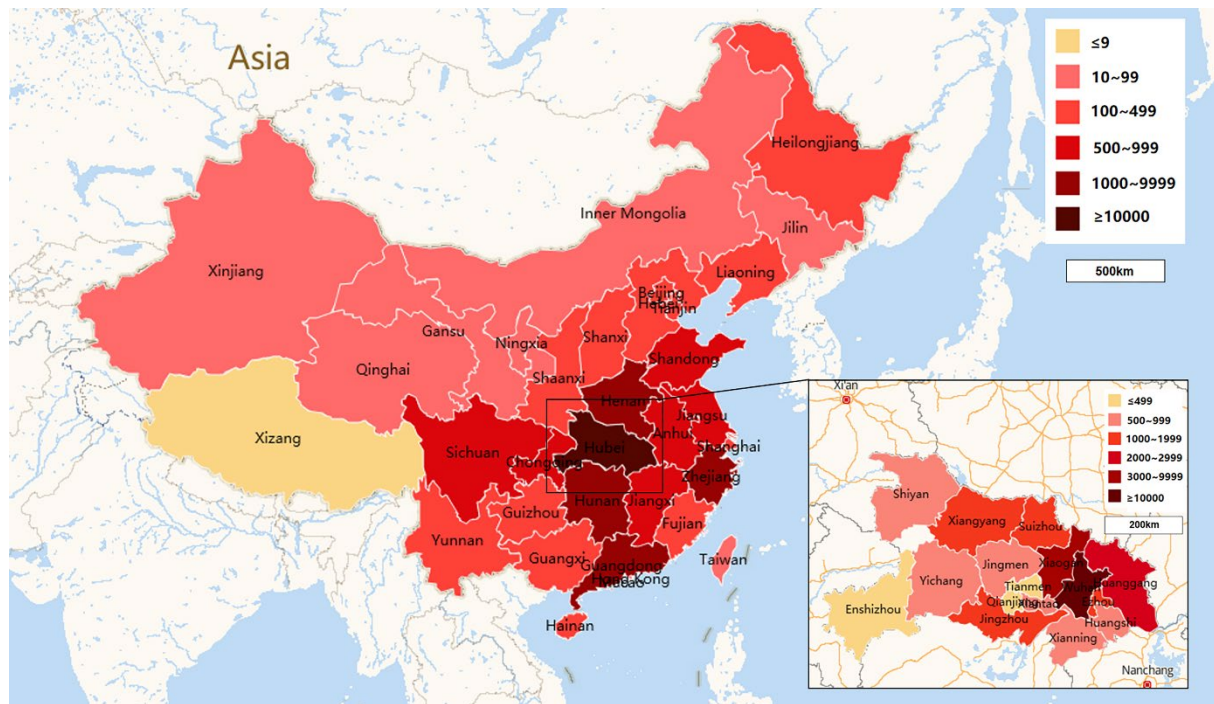
Note.—Plus signs indicate the relative frequency of the findings from the lowest (+) to the highest (+++).

Table 4: Comparison of Common Cold, Influenza, SARS, MERS and Coronavirus Disease 2019 (COVID-19)

Diseases	Respiratory symptoms	Constitutional symptoms	CT imaging findings
Common cold	Stuffy nose, runny noses, sneeze	No obvious discomfort	Usually normal
Influenza⁵²	Stuffy nose, runny noses, sore throat and dry cough	High fever, muscle ache, malaise	Small patch GGO and consolidation with subpleural and/or peribronchial distribution Subpleural GGO and consolidation prominent
SARS^{56,57}	Cough, dyspnea	Fever, chill, malaise, headache, diarrhea	lower lobe involved, interlobular septal and intralobular septal thickening Bilateral, basilar and subpleural airspace, extensive GGO and occasional septal thickening and pleural effusions
MERS^{58,59}	Sore throat, dry cough, dyspnea	Fever, chill, rigor	Multifocal patchy GGOs with subpleural distribution
Mild COVID-19¹²	Cough or not, sore throat	Fever	
Severe COVID-19¹²	Breathless, respiratory failure	Fever, muscle ache, confusion, headache	Diffuse heterogeneous consolidation with GGO

Data from Refs.^{12,52,56-59}

Abbreviations: SARS: severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; GGO: ground-glass opacity



*The situation report includes information provided by national authorities as of 10 AM Central European Time

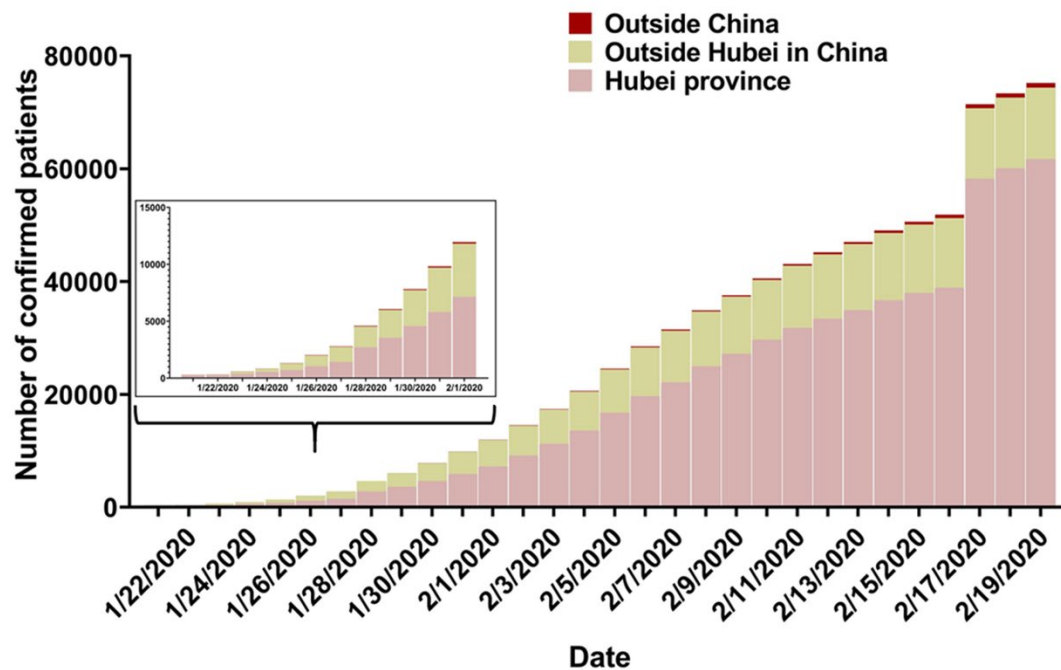
†As reported by China, which includes both laboratory confirmed and clinically diagnosed cases (currently only applicable to Hubei province, China)

Figure 1: Countries, territories, or areas with confirmed cases of Coronavirus Disease 2019 (COVID-19).

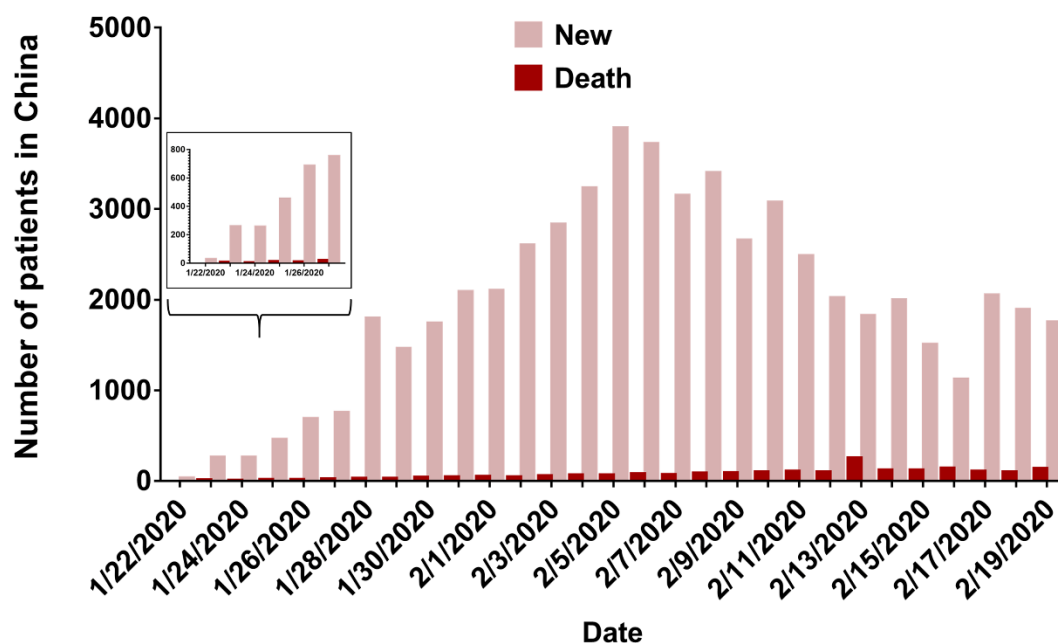
a: The geographic location of patients with confirmed COVID-19 in China, February 19, 2020.

b: Countries, territories or areas with reported confirmed COVID-19, February 19, 2020.

Note.—Data in Panel a is from World Health Organization, National Health Commission of the People's Republic of China; Panel b is adapted from Ref.10.



a



b

Figure 2: Tendency chart of confirmed cases, new cases, and deaths of Coronavirus Disease 2019 (COVID-19)

a: The tendency chart of confirmed patients from Hubei to the areas outside Hubei in China and countries outside China.

b: The tendency chart of new cases of confirmed patients and deaths in China.

Note.—Data are from World Health Organization, National Health Commission of the People's Republic of China. The patients were laboratory-confirmed cases before February, 17, 2020; and included clinically diagnosed cases then.

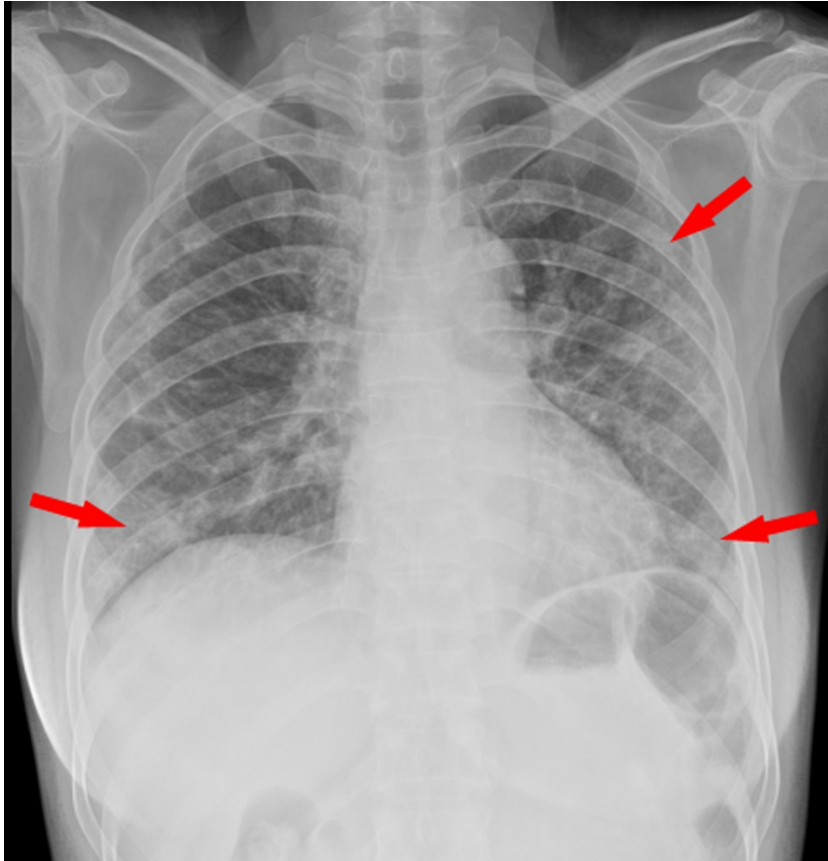
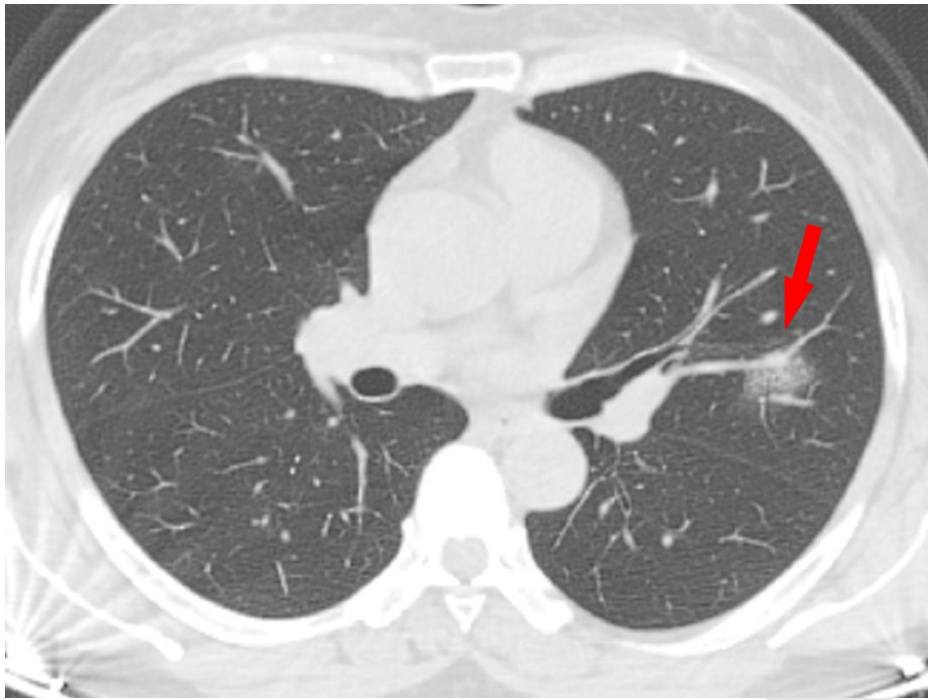
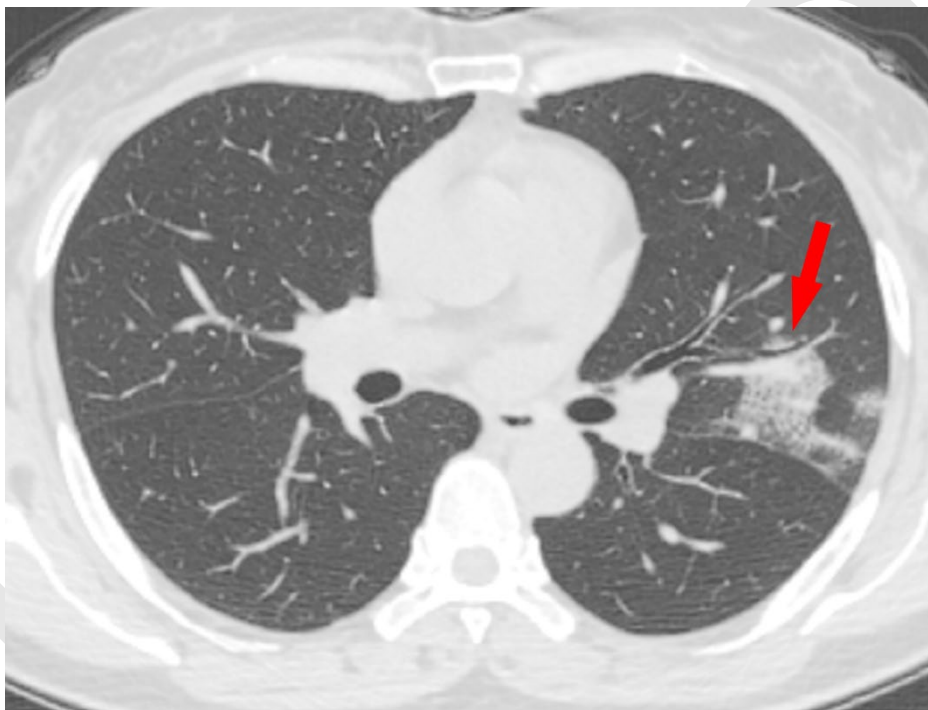


Figure 3: Chest radiography of confirmed Coronavirus Disease 2019 (COVID-19) pneumonia

A 53-year-old female had fever and cough for 5 days. Multifocal patchy opacities can be seen in both lungs (arrows).



a



b

Figure 4: CT findings of confirmed Coronavirus Disease 2019 (COVID-19) pneumonia

Solitary rounded ground-glass opacity (GGO) pattern. A 51-year-old woman presenting without fever had close contact with patients with lab-confirmed COVID-19. a, Baseline axial unenhanced chest CT acquired 6 days before the first positive RT-PCR test showed a rounded GGO in the left lung upper lobe (arrow). b. Follow-up chest CT 4 days later showed the size increase of the lesion (arrow).

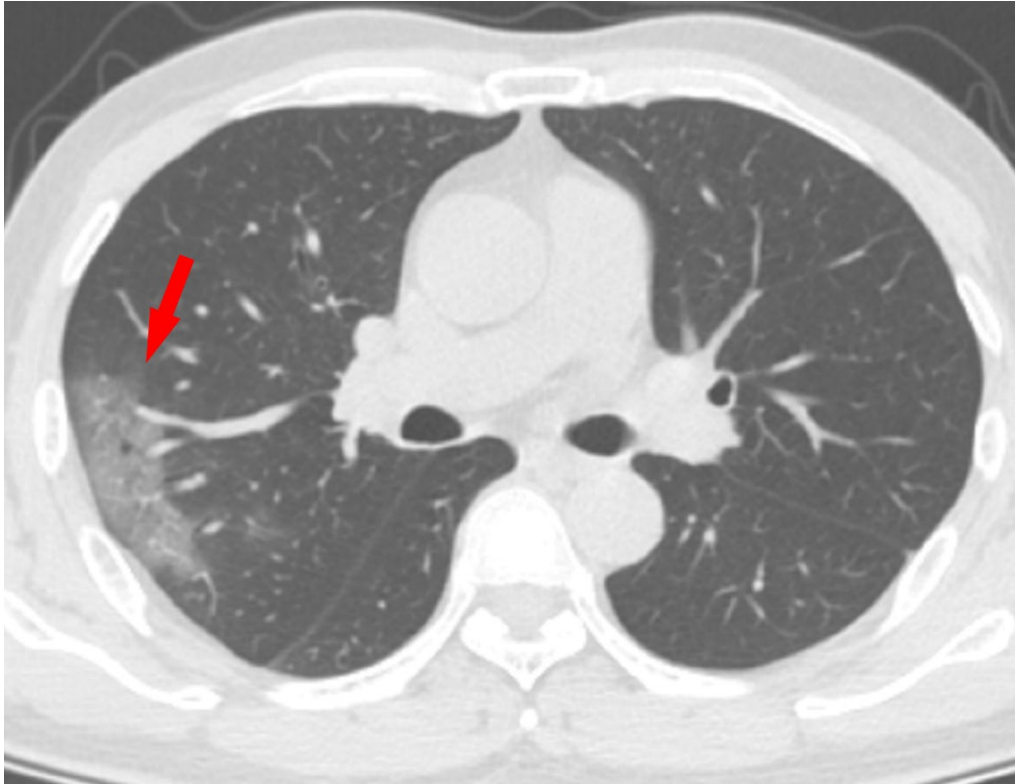
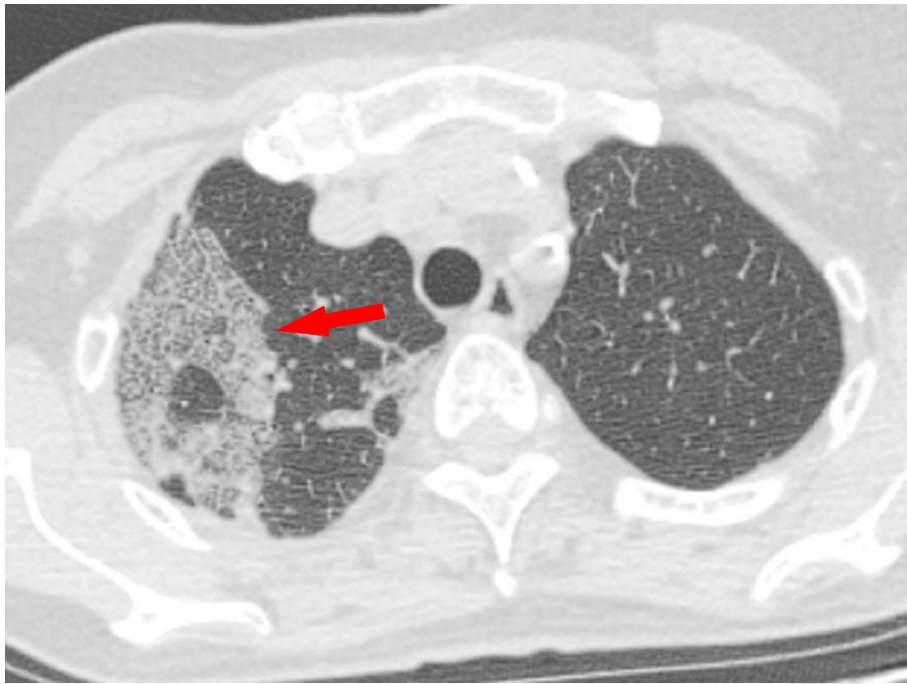
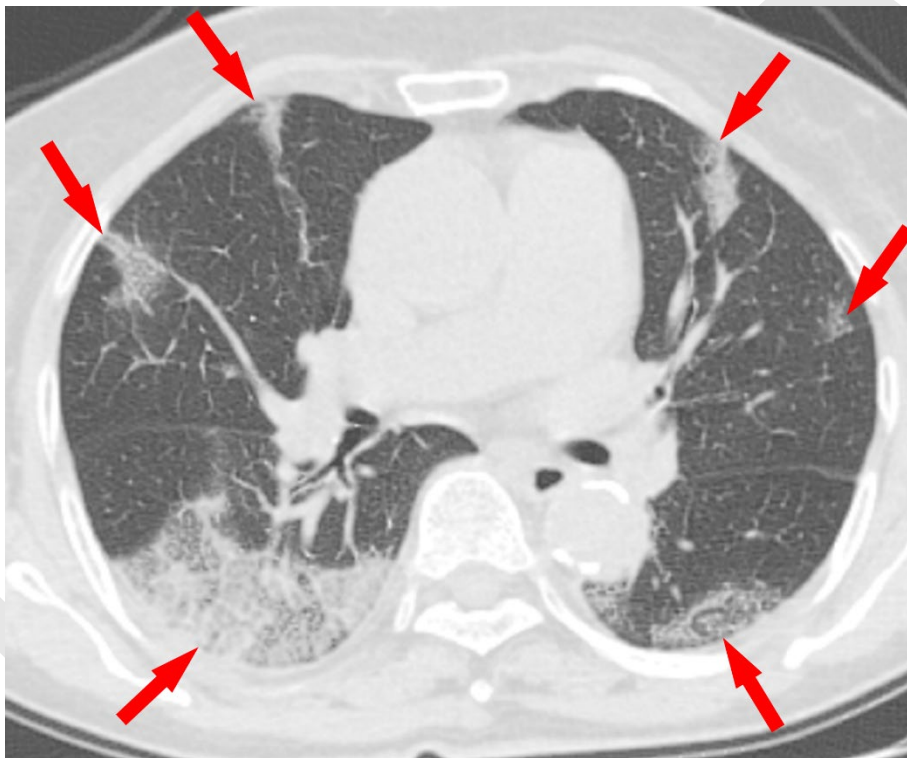


Figure 5: CT findings of confirmed Coronavirus Disease 2019 (COVID-19) pneumonia

Patchy GGO pattern. A 58-old-year man with close contact history presenting without fever. Axial unenhanced chest CT showed patchy pure GGO (arrow).



a



b

Figure 6: CT findings of confirmed Coronavirus Disease 2019 (COVID-19) pneumonia

Crazy paving pattern. A 69-old-year woman presenting with fever, cough, and muscle soreness with Wuhan exposure history. a, Axial unenhanced chest CT acquired on January 26, 2020 showed patchy GGO with typical crazy paving pattern (arrow). b, Axial unenhanced chest CT acquired on January 31, 2020 showed multiple subpleural distributed GGOs (arrows).

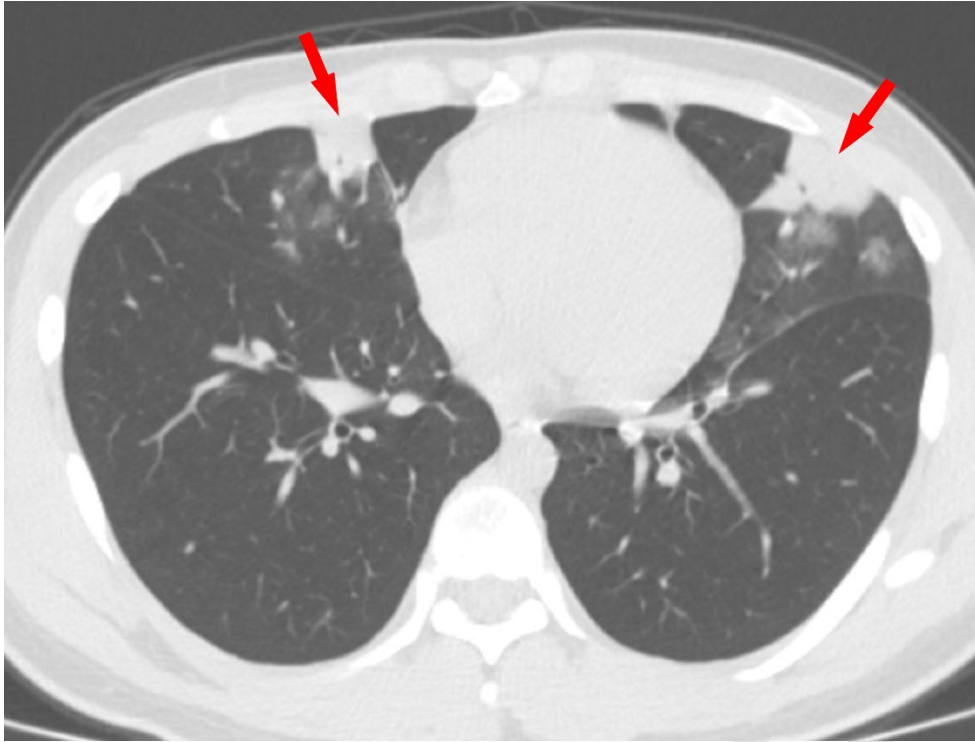


Figure 7: CT findings of confirmed Coronavirus Disease 2019 (COVID-19) pneumonia

Consolidation pattern. A 17-year-old male presented with fever (38.1°C, 100.58°F), cough for three days, and Wuhan exposure history. Axial unenhanced chest CT acquired on January 27, 2020 showed multiple pure consolidation lesions (arrows) in the middle lobe of right lung and upper lobe of left lung.

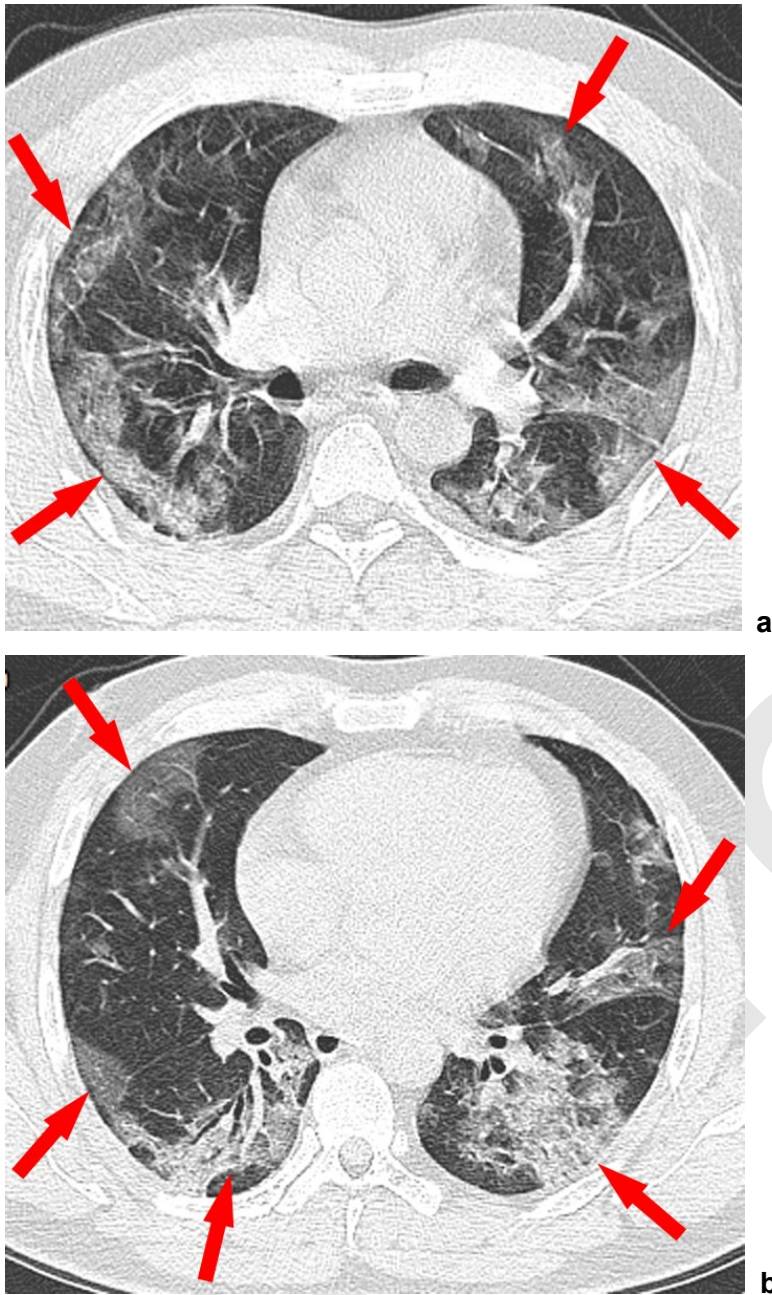
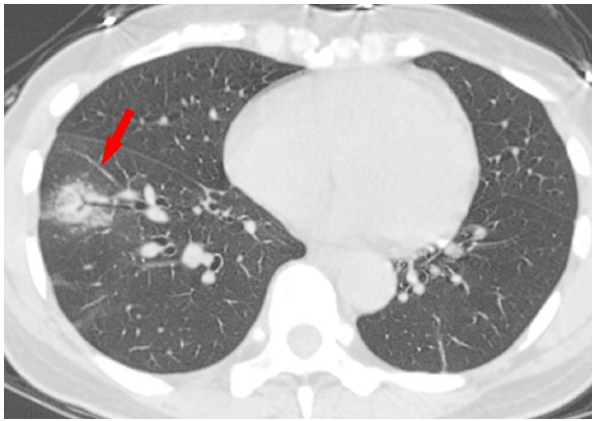
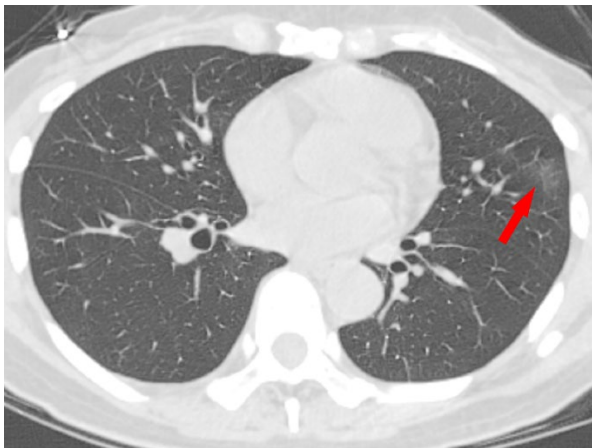


Figure 8: CT findings of severe type confirmed Coronavirus Disease 2019 (COVID-19) pneumonia

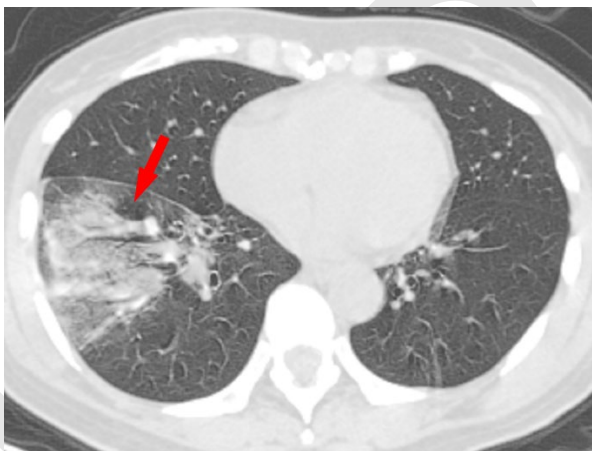
A 43-year-old man presented with no fever and Wuhan exposure history. Axial unenhanced chest CT was acquired on the same day as reverse-transcription–polymerase-chain-reaction. a-b. Two thin slice axial unenhanced chest CT images showed diffusely subpleural distributed ground-glass opacities (arrows). Images provided by courtesy of Dr. Wei Chen, Department of Radiology, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Zhejiang, China.



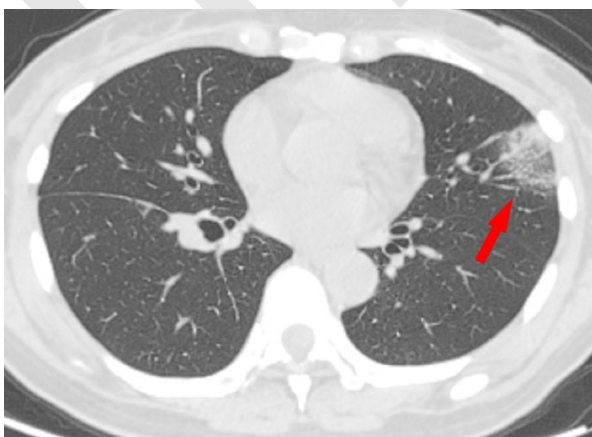
a



b



c



d

Figure 9: CT findings of confirmed Coronavirus Disease 2019 (COVID-19) pneumonia showing disease progression

A 48-year-old woman presented with high fever (39.1 °C, 102.38°F) and Wuhan exposure history. a-b, On January 23, 2020, baseline axial unenhanced chest CT showed ground-glass opacity (GGO) with consolidation in lower lobe of right lung with typical air bronchogram (Panel a, arrow) and one pure GGO (Panel b, arrow) in the upper lobe of left lung. c-d, Three days later, follow-up axial unenhanced chest CT showed the disease progression, appearing as increased extent and consolidation (arrows) compared with baseline chest CT.

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